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Stereoselective Synthesis of (+)-Loline Alkaloid Skeleton

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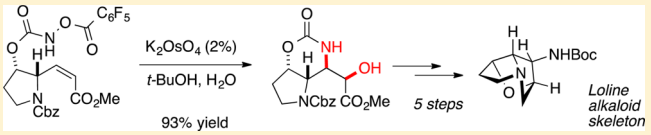
Supporting Information

ABSTRACT: The loline alkaloids present a compact polycyclic pyrrolizidine skeleton and contain a strained five-membered ethereal bridge, structural features that have proven challenging for synthetic chemists to incorporate since the discovery of this natural product family more than 100 years ago. These alkaloids are produced by mutualistic fungal symbionts (endophytes) living on certain species of pasture grasses and protect the host plant from insect herbivory. The asymmetric total synthesis of loline alkaloids is reported and extends our first-generation (racemic) synthesis of this alkaloid family. Key to the synthesis is a diastereoselective tethered aminohydroxylation of a homoallylic carbamate function and a Petasis Borono-Mannich addition.



INTRODUCTION

Four alkaloids—lolines, peramine, ergots, and indole diterpenes—can be produced by mutualistic fungal symbionts (endophytes) living on certain species of pasture grasses (Poaceae; e.g., fescues, ryes).[1] These bioactive alkaloids protect the host plant from invertebrate and vertebrate herbivores. The gene clusters that code for the biosynthesis of all four alkaloids have been determined, which has recently enabled facile determination of the alkaloid profile (by PCR) in most known grass−fungal associations (symbiota).[2] Broad chemotypic variation is observed, and symbionts have been identified that produce between 0 and 3 of these alkaloid families; none have yet been identified that code for production of all four alkaloids.[3] The mutualistic endophytes are ascribed to either of the closely related genera *Epichloae* or *Neotyphodium*. Endophytes from the latter lack the ability to reproduce sexually and are entirely dependent on systemic infection of most tissues, including the seed, in order to facilitate transmission to the next generation. This intriguing evolutionary story of symbiosis has not gone unnoticed, and there are several reviews that encompass the topic.[4]

Of the four natural product families that can arise from grass−endophyte mutualistic associations, ergot alkaloids are the most well-studied owing to their abundant production from a different paradigm, that of the parasitic fungi *Claviceps purpurea*, which infects several cereal grains.[5] Ergot alkaloids such as ergovaline **8** (Figure 1) are believed to function primarily as vertebrate feeding deterrents, but their activity against invertebrate herbivores is known and may be presently underappreciated. The complete roles of the other alkaloid families (lolines, peramine, indole diterpenes) are less well understood. Indole diterpenes (e.g., lolitrem B, Figure 1) are the assumed causative agents of ryegrass staggers, a type of livestock toxicosis.[6] This disorder can develop when ruminants forage on endophyte-infected grass that produces indole diterpene alkaloids. Lolines (e.g., **1**−**5**) and peramine (**6**) are primarily active against insects and show few negative effects on mammalian herbivores. Peramine is present in the largest number of grass−endophyte associations, although the insect feeding deterrent activity of **6** appears modest against most insect species.[7] The loline alkaloids are produced in the greatest abundance of the four protective alkaloid families. In some cases, loline alkaloid content has been observed at more than 10 mg/g of dry endophyte-infected plant material, an amount far in excess of fungal hyphae mass.[8] The loline alkaloids have potent insecticidal activity and antifeedant effects (comparable to nicotine) and have been evaluated against several important commercial insect pest species.[9] Loline (**1**) and the roughly 20 related congeners[10] bearing different substitution at the C1-*exo* amine (see representative examples **2**−**5**) are possibly the most intriguing family due to a rich history, a compact and strained polycyclic structure, and remarkable biological activity, as well as the sense that there is still much left to discover about this alkaloid class.[11]

The chemical history of loline alkaloids began with the isolation of norloline (**3**), originally named temuline, from *Lolium temulentum* in the late 1800s.[12] The loline alkaloids have since been isolated from a variety of grass species (or more specifically, symbiota) and, in at least one case, found in morning glory.[13] Although the fungal endophyte of *L. temulentum* was identified as early as 1904,[14] the protective alkaloids were not explicitly linked to the endophytes until the 1980s.[15,11] The biosynthesis of loline alkaloids has also received significant attention. An informed biosynthetic pathway has emerged through recent efforts at the genomic and biochemical levels and is complemented by extensive isotope precursor feeding studies.[16,11]

Over the past several decades, the loline skeleton has been constructed only a handful of times. The dearth of synthetic routes is perhaps owed to the congested assemblage of structural features of the loline alkaloids and their undesirable physical properties. The tricyclic ring system features a strained ethereal

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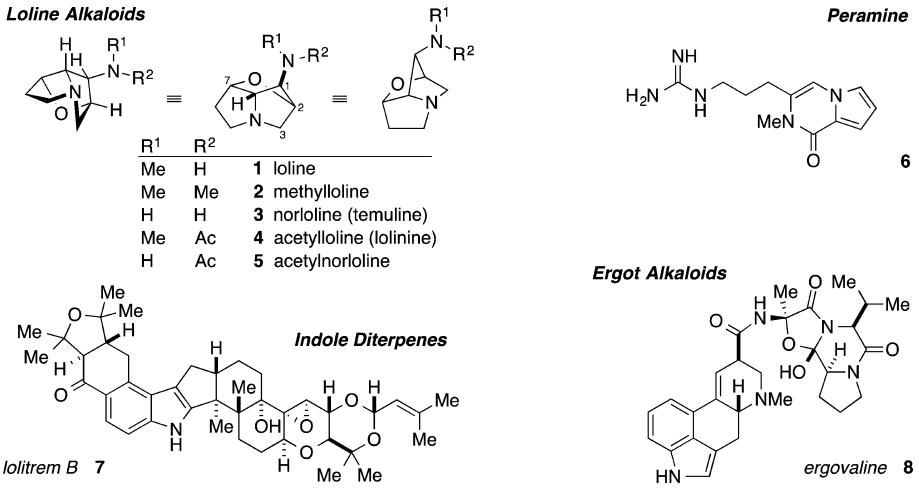
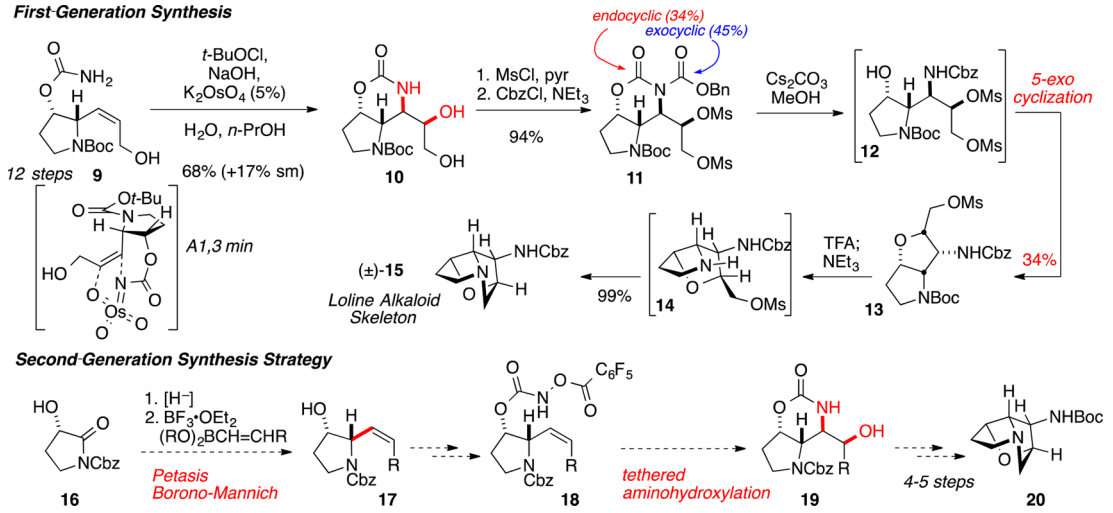


Figure 1. Protective alkaloids from mutualistic grass−fungal endophyte associations.

Scheme 1. Overview of Loline Alkaloid Synthesis and Proposed Revisions



bridge, four contiguous stereogenic centers, and two basic nitrogen atoms. The volatile and basic pyrrolizidine core can prove difficult to handle and readily absorbs CO_2 from the atmosphere to form a zwitterionic carbamate.[17] Two unsuccessful attempts[18] precede the first synthesis of (±)-**1** by Tufariello in 1986.[19] The first asymmetric synthesis followed in 2000 by Blakemore and White.[20] In 2011, both our laboratory[21] and that of Trauner[22] reported, respectively, on the synthesis of (±)- and (+)-loline alkaloids. This article describes the completion of our second-generation synthesis and construction of the (+)-loline core.

RESULTS AND DISCUSSION

An overview of our first-generation synthesis toward the loline alkaloid skeleton is depicted (Scheme 1). In the key operation, a diastereoselective tethered aminohydroxylation (TA) was performed on the homoallylic carbamate **9** using the original reaction conditions reported by Donohoe and co-workers (*t*-BuOCl, NaOH, K_2OsO_4).[23] The resulting product **10** was obtained as a single diastereomer in good yield (68% accompanied by 17% recovered starting material). This reaction serves as one of the only examples of an efficient tethered aminohydroxylation of a homoallylic substrate that employs the original reaction conditions (using hypochlorite as the stoichiometric oxidant). Stereocontrol in the aminohydroxylation event can be rationalized based on nonbonding interactions that minimize allylic ($A^{1,3}$) strain (see 3D depiction of **9**). The *Z*-configuration in **9** is essential for stereocontrol and effective gearing of the amino substituent above the *Re* face of the alkene. The completion of the synthesis from the aminohydroxylation product **10** required only four operations to deliver the loline alkaloid skeleton **15**. After activation of both hydroxyl functions as mesylates and the secondary carbamate as the Cbz mixed imide, the intermediate **11** was subjected to Cs_2CO_3 in methanol. The methanolysis of **11** was not regioselective and afforded products of both endocyclic (desired) and exocyclic imide cleavage. Under the basic reaction conditions, the desired endocyclic cleavage intermediate **12** underwent a subsequent selective 5-*exo* etherification to afford the bicycle **13**. Removal of the pyrrolidine carbamate protection (TFA) and subsequent liberation of the nucleophilic amine (NEt_3) led to *N*-C3 cyclization and delivered the loline alkaloid skeleton **15**.

Although we were successful in our approach, we required quantities of loline alkaloids and related derivatives for biological and biosynthetic investigation that would not be readily accessible given the synthetic route. Revisions were necessary and we aimed for a more concise synthesis and that would provide enantioenriched product. Our first-generation synthesis

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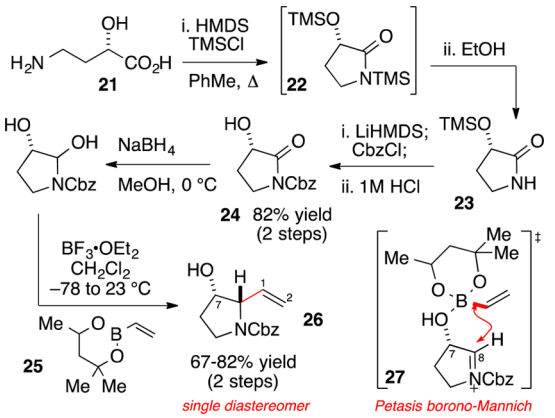
of the loline alkaloids is efficient (4−5 steps) forward from the TA reaction; however, precursor **9** required 12 steps to assemble. A primary goal of the second-generation synthesis was to retain the TA reaction, but access a synthetic equivalent of **9** in fewer steps. We wanted to also preserve several elements of the endgame strategy, in particular the sequence of ring formation where etherification precedes pyrrolizidine formation. In this way, very mild reaction conditions can be employed for the etherification (23 °C, MeOH, Cs_2CO_3). All other syntheses prepare the C2−C7 ethereal bond as the final ring construction, which requires forcing conditions and is often complicated by undesired elimination products.[19,20,22]

Our second-generation synthesis planned to intercept substrates that could take advantage of the more advanced procedures for the TA reaction, namely, the use of a *N*-pentafluorobenzyloxy substituted carbamate (see intermediate **18**), which affords greater yield of product, permits lower catalyst loading, and avoids the use of (and problems associated with) *t*-butyl hypochlorite as a stoichiometric oxidant.[24] Lastly, we anticipated that, by using the Petasis borono-Mannich addition, we could access the necessary *cis*-configured pyrrolidine substrate **17** in short order.

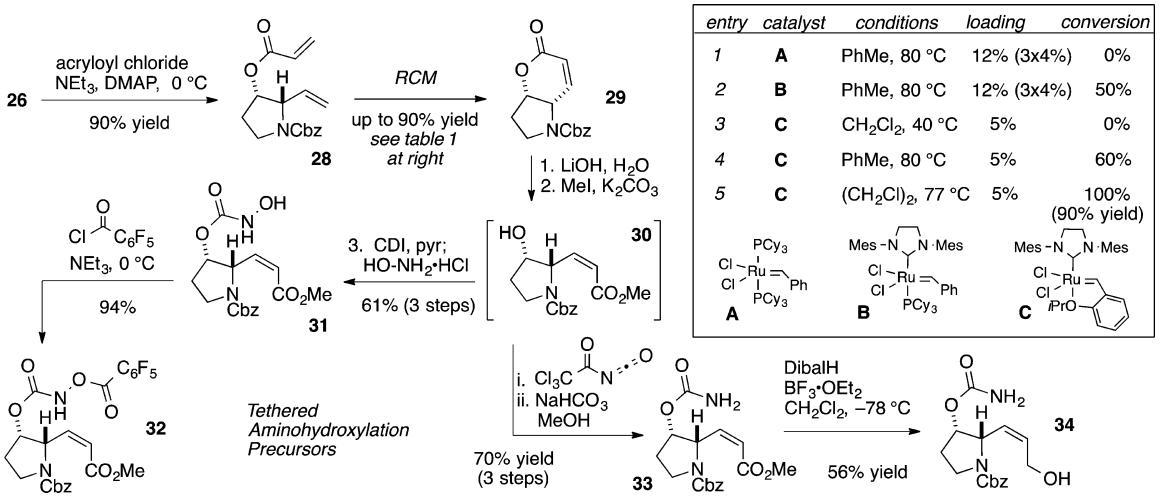
Our second-generation synthesis of the loline alkaloid skeleton started from (*S*)-4-amino-2-hydroxybutanoic acid (**21**), a readily available chiral pool reagent (Scheme 2). Condensation of **21** to pyrrolidinone **22** was promoted with HMDS with catalytic TMSCl.[25] Selective *N*-desilylation of **22** could be conveniently accomplished by addition of ethanol prior to concentration of the reaction mixture. The resulting lactam **23** was deprotonated (0.95 equiv LiHMDS, −78 °C), and the derived lithium amide was captured with CbzCl. Aqueous workup with 1 M HCl removed the TMS silyl ether and revealed the hydroxyl residue in **24**. This reaction sequence leading from **21** to **24** was performed in two reaction vessels, did not require chromatography, and was easily performed on multigram scale. A single recrystallization step afforded **24** in 82% yield over the two operations. Reduction of the imide in **24** ($NaBH_4$, MeOH, 0 °C) preceded diastereoselective Petasis borono-Mannich (PBM) addition.[26] The PBM product **26** is produced as a single diastereomer in good yield (67−82% yield over 2 steps) using methylpentanediol boronate **25**, an air- and chromatographically stable boronate not previously recognized as competent in PBM reactions of this type with *N*-acyliminium ions.[27] Addition of the vinyl residue to C8 through direction of the adjacent C7-hydroxyl is consistent with other PBM reactions and likely occurs through an intermediate resembling **27**.

Two tasks were required to elaborate the Petasis product **26** into a valid TA precursor: (1) The C7-hydroxyl required conversion to an appropriate carbamate functionality, and (2) **26** is lacking one carbon (C3, loline numbering) from the natural product skeleton. This carbon needed to extend the alkene terminus (C2) to create a *Z*-disubstituted alkene. While a modified PBM reaction designed to directly incorporate a *Z*-configured boronate bearing necessary C3 allylic oxygenation (effectively protected to withstand the acidic reaction conditions) was a potential solution, the relative dearth of expeditious methods for construction of such a substrate led us away from this approach. Rather, we turned to a more classical two-step sequence that intercepted lactone **29**, a substrate that closely resembled an intermediate from our first-generation synthesis of the loline alkaloids. Toward this end, the C7-hydroxyl was converted to the α,β-unsaturated ester **28** with acryloyl chloride. Conversion of **28** to the lactone **29** by ring-closing metathesis (RCM) required experimental optimization (see table, Scheme 3). Attempted RCM with Grubbs first-generation catalyst (**A**) afforded only starting material. We were able to observe some product with Grubbs second-generation

Scheme 2. Construction of Pyrrolidine Core via Petasis Borono-Mannich Addition



Scheme 3. Preparation of Cbz-Protected Aminohydroxylation Precursors



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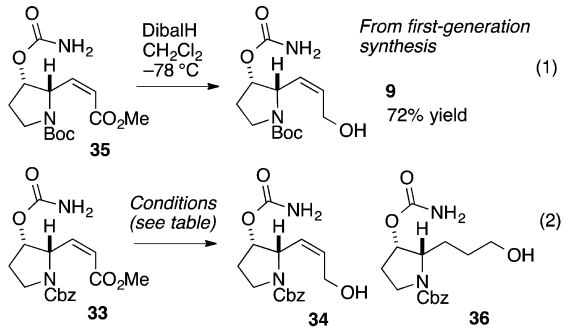
catalyst (**B**) at high catalyst loading (3 additions of 4 mol %; 12 mol % total) in toluene at 80 °C, albeit with relatively low conversion (ca. 50%, entry 2). The Hoveyda−Grubbs catalyst **C** showed improved turnover. Although no reaction was detected with **C** in CH_2Cl_2 at 40 °C (entry 3), at more elevated temperatures (toluene 80 °C), greater conversion to product was observed. Further reaction optimization revealed that $(CH_2Cl)_2$ was a superior solvent for this metathesis. In practice, addition of catalyst **C** (5 mol %) to a preheated solution of **28** in $(CH_2Cl)_2$ at reflux led to 100% conversion and reliably afforded a 90% isolated yield of lactone **29**.

Hydrolysis of the lactone in **29** with aqueous LiOH gave the derived carboxylate and alkylation with MeI afforded the *Z*-*α*,*β*-unsaturated ester **30**. Attempts to convert the lactone **29** directly to ester **30** (NaOMe in MeOH, or K_2CO_3 in MeOH, or NEt_3 in MeOH) led to undesired products resulting from hetero-conjugate addition or epimerization at the *γ*-position. The unsaturated ester **30** was reasonably slow to relactonize and permitted conversion of the hydroxyl moiety into a carbamate functional group. In preparation for the advanced procedure for the TA reaction, the *N*-pentafluorobenzyloxy substituted carbamate **32** was prepared via the intermediate *N*-hydroxy carbamate **31**. From lactone **29**, the pentafluorobenzyloxy carbamate **32** was prepared in 4 steps (2 chromatographic separations) in 57% overall yield. The primary carbamate could be prepared in a 3-step sequence using trichloroacetyl isocyanate, followed by hydrolysis of the intermediate imide to give **33** in 70% yield from lactone **29**.

Although **33** is a potential substrate for aminohydroxylation, we knew from our earlier work with the related Boc-protected precursor **35** (Scheme 4) that TA reaction would be

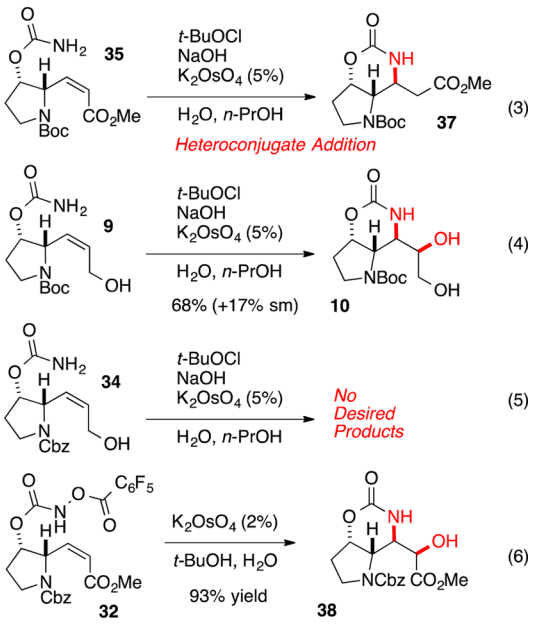
Scheme 4. Reduction of *Z*-*α*,*β*-Unsaturated Ester



	reaction conditions		product (yield)		
1	DibalH (3 equiv) −78 °C	1h	**34** (5%)	-	
2	$LiBH_4$ −78 °C to RT	17h	**34** (12%)	**36** (55%)	
3	$LiAlH_4$ −78 °C to −10 °C	3h	**34** (26%)	**36** (22%)	**33** (15%)
4	$LiBEt_3H$ −78 °C to −40 °C	3.5h	**34** (16%)	**36** (5%)	**33** (15%)
5	DibalH (4 equiv) BF_3·OEt_2 (3 equiv) CH_2Cl_2, −78 °C	0.5h	**34** (56%)	-	

unsuccessful. Attempted TA reaction with **35** (*t*-BuOCl, NaOH, K_2OsO_4) gave **37** as the only product, a result of intramolecular heteroconjugate addition of the carbamate to the unsaturated ester (Scheme 5, eq 3). The undesired conjugate addition pathway in **35** was avoided by tempering the electrophilic nature of the alkene. Reduction of the ester in **35** (Dibal, −78 °C) proceeded cleanly and gave allylic alcohol **9**

Scheme 5. Tethered Aminohydroxylation Reactions



(Scheme 4, eq 1). This substrate (**9**) underwent efficient TA reaction to afford **10** (Scheme 5).

A similar reduction was planned for the Cbz-protected unsaturated ester **33** (Scheme 4, eq 2); however, reduction under the same conditions (Dibal, −78 °C) proved more complicated. Under these conditions, consumption of **33** was observed (as evident by TLC), but following aqueous workup, only a small amount of the allylic alcohol **34** was apparent (5% yield). The bulk of the reaction mixture contained predominantly aldehyde-derived products. On the basis of this observation, we reasoned that reduction was incomplete and the tetrahedral intermediate derived from *N*-Cbz-protected **33** was considerably more stable than the corresponding tetrahedral intermediate derived from *N*-Boc-protected **35**. Increasing the reaction duration (up to 8 h) or reaction temperature did not noticeably encourage collapse of the tetrahedral intermediate and, at temperatures above −40 °C, the Cbz-carbamate became reactive toward the reductant. A brief survey of other hydride sources did not provide an efficient nor selective reduction. Alternative hydride sources ($LiBH_4$; $LiAlH_4$; $LiBEt_3H$) all afforded significant quantities of the saturated alcohol **36** in addition to the desired allylic alcohol **34** (see table, entries 2−4, Scheme 4). Fortunately, reduction with Dibal (4 equiv) in the presence of BF_3·OEt_2 (3 equiv) at −78 °C (see table, entry 5, Scheme 4) afforded the desired alcohol **34** as the only product in 56% isolated yield (unoptimized).

With a serviceable method to prepare **34** confirmed, we attempted the key aminohydroxylation. As with the aforementioned reduction, the Cbz protection appeared to significantly alter the reactivity of this substrate as compared to the Boc-protected derivative. While TA reaction with Boc-protected **9** proceeded well (Scheme 5, eq 4), the analogous reaction with Cbz-protected **34** (eq 5) afforded none of the desired aminohydroxylation product.

Fortunately, the advanced procedures for the TA reaction with the *N*-pentafluorobenzyloxy functionalized carbamate **32** cleanly achieved the desired transformation, and product **38** was observed as a single diastereomer in excellent yield (Scheme 5, eq 6).

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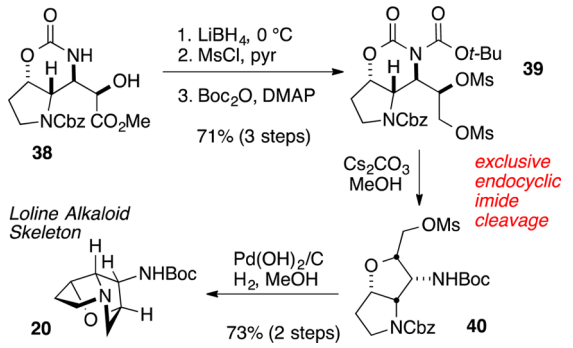
From the TA product **38**, five operations were required to construct the loline alkaloid core (Scheme 6). The correct

Scheme 6. Completion of Loline Alkaloid Skeleton



oxidation state at C3 was installed by reduction of the ester in **38** with $LiBH_4$. The resulting intermediate diol was primed as the bis-mesylate, and the carbamate was activated as the mixed imide **39**. Imide **39** underwent selective cleavage of the *t*-butoxy carbamate (with Cs_2CO_3 in MeOH) and subsequent 5-exo etherification to give the bicyclic core **40** as the only observed product. The exclusive selectivity for endocyclic carbamate cleavage with imide **39** is notable. Carbamate cleavage with the related mixed imide (possessing benzyl substituent) provided both endo- and exocyclic cleavage products (see intermediate **11**, Scheme 1). Removal of the Cbz-group in **40** by hydrogenolysis with Perlman's catalyst revealed the nucleophilic secondary amine, which underwent spontaneous *N*-C3 cyclization to establish the pyrrolizidine core and loline tricyclic framework. The resulting product, *N*-Boc norloline (**20**), was identical to material previously prepared by Trauner and co-workers.[22]

Conversion of **20** into two loline natural products has been accomplished, and because the interconversion of several loline congeners is known, the synthesis of **20** represents a formal total synthesis of many of the loline alkaloids in this natural product family.[10,22] Our second-generation synthesis of the loline core is characterized by several highly diastereo- and regioselective reactions. The tethered aminohydroxylation was the reaction of greatest strategic importance to the synthesis. This synthesis demonstrates the ability to use the TA reaction to deliver the nitrogen and oxygen functionalities with excellent stereo- and regiocontrol. Additionally, the TA reaction offers a direct route to rapidly construct the four contiguous stereogenic centers in the molecule, arguably one of the more intricate features of the loline skeleton. The unsuccessful aminohydroxylation reactions highlighted in Scheme 5 (eqs 3 and 5) offer additional fodder as to the capricious nature of the original TA reaction conditions that employ *t*-BuOCl to generate *in situ* the reactive *N*-chlorocarbamate.[24] The successful TA reactions (eqs 4 and 6) provide another valuable demonstration that this reaction sequence can be applied in complex contexts.[28] In particular, the successful transformation of **32** to **38** (eq 6) illustrates the important advance Donohoe and co-workers have achieved by extension of this chemistry to include the *N*-pentafluorobenzyloxy carbamate substrates.

The described synthesis route can deliver a sufficient quantity of loline alkaloids in order to begin to address questions of biological, biosynthetic, and pharmacological importance as well as to deconvolute the remarkable plant−fungus−herbivore tripartite relationship. Results from these ongoing efforts will be reported in due course.

EXPERIMENTAL SECTION

Experimental conditions and spectral data were published previously for compounds **9**−**15**.[21]

Benzyl (*S*)-3-Hydroxy-2-oxopyrrolidine-1-carboxylate (24). Chlorotrimethylsilane (0.270 mL, 2.1 mmol, 0.05 equiv) was added to a mixture of (*S*)-4-amino-2-hydroxybutanoic acid **1** (5.00g, 42.0 mmol), xylene (100 mL), and HMDS (61.5 mL, 294 mmol, 7.0 equiv) at rt. The reaction mixture was heated to reflux for 12 h, cooled to rt, and diluted with absolute ethanol (200 mL). The solvents were removed under reduced pressure to afford lactam **23** (7.30 g, quant recovery) as a tan solid, which was used without further purification. Spectral data for lactam **23** match published data.[26] A portion of this material, (*S*)-3-((trimethylsilyl)oxy)pyrrolidin-2-one (**23**) (3.27 g, 19.6 mmol), was dissolved in THF (75 mL) at −78 °C, and LiHMDS (1.0 M soln in THF, 18.6 mmol, 0.95 equiv) was added dropwise over 5 min. After stirring for 0.5 h at −78 °C, CbzCl (3.50 g, 20.56 mmol, 1.05 equiv) was added to the reaction dropwise over 5 min. The solution was warmed to 23 °C over 1 h and quenched with 1.0 M aqueous HCl (30 mL). The reaction mixture was poured into a separatory funnel and extracted with ethyl acetate (3 × 30 mL). The organic layers were combined, washed with brine (2 × 30 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting white powder was purified by recrystallization (EtOAc/hexanes) to afford the desired product **24** (3.66 g, 82% yield) as a white powder: mp 99.8−100.7 °C: TLC (60% EtOAc in hexanes), R_f: 0.70 (UV, CAM); $[\alpha]_D^{25} = -63.9$ (*c* 1.94, CH_2Cl_2); IR (film) 3448, 3085, 3028, 2989, 2879, 1778, 1689, 1385, 1282, 1227 cm^{-1}. Spectra of **24** are complicated by imide rotamers. ^1H NMR (400 MHz, CDCl3) δ 7.40 (m, 5H), 5.29 (s, 2H), 4.38 (m, 1H), 3.89 (m, 1H), 3.60−3.53 (td, *J1* = 6.6 Hz, *J2* = 10.5 Hz, 1H), 2.48−2.42 (m, 1H), 2.00−1.94 (m, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 174.4, 151.1, 134.9, 128.6, 128.5, 128.2, 77.2, 70.4, 68.3, 42.1, 27.0; HRMS (ES^+): Exact mass calcd for $C_{12}H_{13}NO_4Na^+$[M + Na]$^+$, 258.0737. Found 258.0734.

Benzyl (2*S*,3*S*)-3-Hydroxy-2-vinylpyrrolidine-1-carboxylate (26). To a solution of imide **24** (0.670 g, 2.85 mmol) in MeOH (20 mL) at 0 °C was added $NaBH_4$ (55 mg, 1.43 mmol, 0.5 equiv) in one portion. After stirring for 0.5 h at 0 °C, the reaction was quenched with sat. $NaHCO_3$ (20 mL) and the mixture was concentrated to remove the bulk of MeOH. The mixture was transferred to a separatory funnel and extracted with EtOAc (3 × 20 mL). The organic portions were combined, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The desired reduction product (0.675 g, 2.84 mmol, 99% yield) was obtained as a white powder and used directly in the subsequent reaction without further purification: TLC (60% EtOAc in hexanes), R_f: 0.40 (UV, CAM). Spectral data for benzyl (3*S*)-2,3-dihydroxypyrrolidine-1-carboxylate match published data.[26] To a solution of benzyl (3*S*)-2,3-dihydroxypyrrolidine-1-carboxylate (0.675 g, 2.85 mmol) and vinyl boronate **25** (0.482 g, 3.13 mmol, 1.1 equiv) in CH_2Cl_2 (20 mL) at −78 °C was added dropwise $BF_3{\cdot}Et_2O$ (1.40 mL, 11.4 mmol, 4 equiv). The solution was warmed to 0 °C for 2 h and stirred at room temperature for an additional 3 h. The reaction was quenched with sat. $NaHCO_3$ (20 mL), and the mixture was transferred to a separatory funnel. The organic layer was removed, and the aqueous layer was extracted with chloroform (3 × 5 mL). The organic fractions were combined and washed with brine (50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting yellow oil was purified by flash column chromatography on silica gel (elution: 20 → 80 EtOAc in hexanes) to afford **26** (506 mg, 72% yield over the two steps) as a clear oil: TLC (60% EtOAc in hexanes), R_f: 0.40 (UV, CAM); $[\alpha]_D^{25} = -1.09$ (*c* 0.93, CH_2Cl_2); IR (film) 3419, 3083, 3072, 3033, 2978, 2951, 2894, 2361, 1956, 1698, 1592, 1540, 1480, 1448, 1357, 1257, 1213 cm^{-1}. The spectra of **26** are complicated by carbamate rotamers. ^1H NMR (400 MHz, $CDCl_3$) 7.33 (m, 5H), 5.81 (m, 1H), 5.22 (m, 2H), 5.09 (m, 2H), 4.35 (m, 2H), 3.56 (m, 2H), 2.23 (1H), 2.06 (m, 1H), 1.88 (m, 1H); ^{13}C (100 MHz, $CDCl_3$) δ 136.6, 133.9, 133.5, 128.4, 128.3, 127.8, 118.2, 117.9, 72.3, 71.8, 66.7, 62.9, 62.3, 43.7, 31.6 30.8; HRMS (ES^+): Exact mass calcd for $C_{14}H_{17}NO_3Na^+$ [M + Na]$^+$, 270.1100. Found 270.1099.

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Benzyl (2*S*,3*S*)-3-(Acryloyloxy)-2-vinylpyrrolidine-1-carboxylate (28). Homoallylic alcohol **26** (357 mg, 1.45 mmol) was added to a flame-dried flask. After flushing the vessel with N_2, the substrate was dissolved in CH_2Cl_2 (6 mL) and iPr_2NEt (1.26 mL, 7.23 mmol) and DMAP (12 mg, 0.072 mmol) were added and the reaction flask was cooled to −78 °C. In a separate flame-dried pear-shaped flask, acryloyl chloride (0.36 mL, 4.35 mmol) was diluted with CH_2Cl_2 (3 mL). The acryloyl chloride solution was added dropwise over 10 min via cannula. After stirring for 1 h at −78 °C, the reaction was warmed to rt for 0.5 h and then quenched with 1 M HCl (10 mL). The mixture was transferred to a separatory funnel, and the organic layer was removed. The aqueous portion was extracted with CH_2Cl_2 (3 × 10 mL). The organic portions were combined, washed with $NaHCO_3$ (20 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel (elution: 10% → 45% EtOAc in hexane) to afford **28** (394 mg, 90% yield) as a pale yellow oil: TLC (40% EtOAc in Hexanes), R_f: 0.50 (UV, CAM); $[\alpha]_D^{25}$ = −37.9 (*c* 1.19, CH_2Cl_2); IR (film) 3066, 3033, 2985, 2955, 2892, 2361, 2339, 1723, 1703, 1635, 1406, 1355, 1296, 1267, 1190, 1129, 1106, 1069, 1052 cm^{-1}. The spectra of **28** are complicated by carbamate rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 6.42−6.38 (d, J = 17.2, 1H), 6.13−6.06 (dd, J_1 = 17.2 Hz, J_2 = 10.2 Hz, 1H), 5.85−5.82 (d, J = 10.2 Hz, 1H), 5.68 (br. s., 1H), 5.25−5.08 (m, 5H), 4.67−4.63 (t, J = 6.6 Hz, 1H), 3.58−3.47 (m, 2H), 2.24−2.17 and 2.07−1.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 136.5, 132.5, 131.4, 127.9, 117.4, 73.4, 66.8, 60.6, 43.1, 28.2; HRMS (ES^+): Exact mass calcd for $C_{17}H_{19}NO_4Na^+$ $[M + Na]^+$, 324.1206. Found 324.1204.

Benzyl (3a*S*,7a*S*)-5-Oxo-3,3a,5,7a-tetrahydropyrano[3,2-*b*]-pyrrole-1(2*H*)-carboxylate (29). Compound **28** (294 mg, 0.98 mmol) was added to a flame-dried two-neck flask, fitted with a reflux condenser and flushed with N_2. Dichloroethane (19.7 mL) was added, and the reaction mixture was heated to reflux 77 °C (bath temp. 85 °C) for 10 min. Hoveyda−Grubbs second-generation catalyst was added (45 mg, 0.068 mmol) in one potion. After stirring at reflux for 15 h under N_2, the reaction mixture was cooled to rt and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel (elution: 15% → 70% EtOAc in hexane) to afford **29** (242 mg, 90% yield) as a brown oil: TLC (60% EtOAc in Hexanes), R_f: 0.40 (UV, CAM); $[\alpha]_D^{25}$ = +228 (*c* 0.19, CH_2Cl_2); IR (film) 3063, 2955, 2892, 2361, 2339, 1729, 1700, 1555, 1418, 1358, 1333, 1249, 1207, 1109, 1047 cm^{-1}. The spectra of **29** are complicated by carbamate rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 7.23−7.19 and 6.91−6.87 (dd, J_1 = 10.2 Hz, J_2 = 4.8 Hz, 1H), 6.07−6.01 (t, J = 10.2 Hz, 1H), 5.21−5.06 (m, 3H), 4.32 (s, 1H), 3.72−3.67 and 3.63−3.56 (m, 2H), 2.28−2.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 154.5, 142.3, 136.1, 128.4, 127.9, 120.9, 79.2, 67.3, 51.3, 44.6, 31.2; HRMS (ES^+): Exact mass calcd for $C_{15}H_{15}NO_4Na^+$ $[M + Na]^+$, 296.0893. Found 296.0894.

Benzyl (2*S*,3*S*)-3-(Carbamoyloxy)-2-((*Z*)-3-methoxy-3-oxoprop-1-en-1-yl)pyrrolidine-1-carboxylate (33). To a solution of lactone **29** (283 mg, 1.03 mmol) in THF (5.3 mL) and H_2O (1.7 mL) was added $LiOH·H_2O$ (54 mg, 1.29 mmol, 1.25 equiv) at rt. After stirring for 1 h, the reaction mixture was transferred to a separatory funnel and partitioned between 0.2 M HCl (10 mL) and EtOAc (5 mL). The organic layer was removed, and the aqueous layer was extracted with additional EtOAc (4 × 5 mL). The organic fractions were combined and washed with brine (40 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was dissolved in DMF (5 mL) at rt, and K_2CO_3 (171 mg, 1.24 mmol, 1.2 equiv) and MeI (0.64 mL, 10.3 mmol, 10.0 equiv) were added. After stirring for 2 h, the reaction mixture was transferred to a separatory funnel and diluted with a brine and 1.0 M HCl solution (10 mL, 10:1 brine:HCl) and extracted with $CHCl_3$ (5 mL). The organic layer was removed, and the aqueous layer was extracted with $CHCl_3$ (4 × 5 mL). The organic layers were combined, washed with brine (40 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. Trichloroacetyl isocyanate (0.182 mL, 1.55 mmol. 1.5 equiv) was added, and the reaction was stirred for 30 min and concentrated *in vacuo*. The residue was dissolved in MeOH (4.0 mL) and H_2O (1.0 mL) and cooled to 0 °C. To this solution was added $NaHCO_3$ (173 mg, 2.06 mmol, 2 equiv), and the reaction was allowed to warm to rt overnight. The reaction mixture was transferred to a separatory funnel and partitioned between brine (5 mL) and $CHCl_3$ (5 mL). The organic layer was removed, the aqueous layer was extracted with $CHCl_3$ (4 × 5 mL), and the organic layers were combined, washed with brine (40 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was purified by flash column chromatography (elution: 40% → 80% EtOAc in hexanes) to afford **33** (243 mg, 70% yield over 3 steps) as a white solid: TLC (60% EtOAc in hexanes), R_f: 0.30 (UV, CAM); $[\alpha]_D^{25}$ = +81.9 (*c* 1.67, CH_2Cl_2); IR (film): 3399, 2954, 2885, 1715, 1689, 1606, 1415, 1348, 1198, 1172, 1105, 1043 cm^{-1}. The spectra of **33** are complicated by carbamate rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 6.17 (m, 1H, 5.87 (m, 1H, J = 10.9 Hz), 5.54 (s, 2H), 5.10 (m, 4H), 3.67 (m, 4H), 3.56 (m, 1 H), 2.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 155.7, 154.9, 146.4, 136.4, 128.2, 127.9, 127.7, 127.6, 120.2, 77.3, 76.2, 75.7, 66.8, 59.5, 58.4, 51.3, 51.2, 45.0, 44.7, 31.2, 30.6 HRMS (ES^+): Exact mass calcd for $C_{17}H_{20}N_2O_6Na^+$ $[M + Na]^+$, 371.1214. Found 371.1215.

Benzyl (2*S*,3*S*)-3-(Carbamoyloxy)-2-((*Z*)-3-hydroxyprop-1-en-1-yl)pyrrolidine-1-carboxylate (34). Unsaturated ester **33** (187 mg, 0.54 mmol) was dissolved in CH_2Cl_2 (7.2 mL). After cooling to −78 °C, $BF_3·OEt_2$ (0.23 mL, 1.86 mmol, 3.5 equiv) was introduced over 5 min and stirred at −78 °C for an additional 5 min. A solution of Dibal-H (0.5 M in CH_2Cl_2, 4.32 mL, 2.16 mmol) was added dropwise over 10 min. After 0.5 h, the reaction was quenched with EtOAc (1 mL) and stirred for 5 min. The reaction was warmed to rt and diluted with conc. HCl (5 mL) and stirred for 5 min to dissolve aluminum salts. The mixture was transferred to a separatory funnel with EtOAc (10 mL), and the organic layer was removed. The aqueous portion was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with sat. aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel (elution: 55% → 100% EtOAc in hexane) to afford **34** (96 mg, 56% yield) as a white solid: TLC (80% EtOAc in Hexanes), R_f: 0.25 (UV, CAM); $[\alpha]_D^{25}$ = −42.2 (*c* 1.06, CH_2Cl_2); IR (film) 3816, 3406, 3213, 2953, 1696, 1421, 1344, 1207, 1086 cm^{-1}. The spectra of **34** are complicated by carbamate rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5H), 5.96 (m, 1H), 5.74 (m, 1H), 5.43−5.29 (m, 1H), 5.12−5.05 (m, 4H), 4.34 (m, 1H), 4.05 and 3.74 (m, 2H), 2.37 (br. s), 2.19−2.16 and 2.06−2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 154.6, 136.2, 132.7, 128.8, 128.5, 127.8, 127.5, 125.7, 74.2, 73.2, 67.1, 55.3, 43.3, 29.2; HRMS (ES^+): Exact mass calcd for $C_{16}H_{20}N_2O_5Na^+$ $[M + Na]^+$, 343.1264. Found 343.1266.

Benzyl (2*S*,3*S*)-3-(Carbamoyloxy)-2-(3-hydroxypropyl)-pyrrolidine-1-carboxylate (36). TLC (60% EtOAc in Hexanes), R_f: 0.30 (UV, CAM); $[\alpha]_D^{25}$ = +30.7 (*c* 1.5, CH_2Cl_2); IR (film) 3337, 2942, 1692, 1611, 1422, 1344, 1199, 1086, 1052 cm^{-1}. The spectra are complicated by carbamate rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.10 (m, 2H), 4.98 (m, 1H), 3.68 (m, 2H), 3.45 (m, 2H), 2.12 (m, 2H), 2.01 (m, 2H), 1.85 (m, 1H), 1.68 (m, 2H), 1.58 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 155.3, 136.6, 128.5, 128.0, 73.6, 66.9, 62.7, 51.6, 43.5, 29.9, 28.1, 25.0; HRMS (ES^+): Exact mass calcd for $C_{16}H_{22}N_2O_5Na^+$ $[M + Na]^+$, 345.1421. Found 345.1420.

Benzyl (2*S*,3*S*)-3-((Hydroxycarbamoyl)oxy)-2-((*Z*)-3-methoxy-3-oxoprop-1-en-1-yl)pyrrolidine-1-carboxylate (31). To a solution of lactone **29** (1.50 g, 5.50 mmol) in THF (15 mL) and H_2O (5 mL) was added $LiOH·H_2O$ (280 mg, 6.8 mmol, 1.25 equiv) at rt. After stirring for 1 h, the reaction mixture was transferred to a separatory funnel and partitioned between 0.2 M HCl (30 mL) and EtOAc (20 mL). The organic layer was removed, and the aqueous layer was extracted with additional EtOAc (4 × 10 mL). The organic portions were combined and washed with brine (40 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was dissolved in DMF (5 mL) at rt, and K_2CO_3 (0.85 g, 6.6 mmol, 1.2 equiv) and MeI (1.25 mL, 20 mmol) were added. After stirring for 1 h, the reaction mixture was transferred to a separatory funnel and diluted with a brine (20 mL) and 1.0 M HCl solution (6 mL) and extracted with $CHCl_3$ (10 mL). The organic layer was removed, and the aqueous layer was extracted with $CHCl_3$ (4 × 10 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was dissolved in

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pyridine (12 mL), and CDI (1.78 g, 11 mmol) was added in one portion. After stirring for 12 h at rt, the reaction was cooled to 0 °C and H_2NOH·HCl (1.50 g, 21.4 mmol) was added, and the reaction was allowed to warm slowly to rt over 5 h. The reaction mixture was diluted with 0.5 M HCl (50 mL), transferred to a separatory funnel, and extracted with EtOAc (4 × 20 mL). The combined organic portions were washed with brine (40 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel (elution: 30% → 100% EtOAc in hexane) to afford the desired *N*-hydroxy carbamate **31** (1.22 g, 61% over 3 steps) as a colorless oil: TLC (60% EtOAc in Hexanes), R_f: 0.20 (UV, CAM); $[\alpha]_D^{25}$ = +71.3 (*c* 1.03, CH_2Cl_2); IR (film) 3303, 3066, 3032, 2993, 2954, 2898, 1714, 1617, 1539, 1455, 1357, 1255, 1199, 1110, 1034, 996, 918, 816, 765, 733, 699, 667 cm^{-1}. The spectra of **31** are complicated by carbamate rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75−7.71 (d, *J* = 18.8 Hz, 1H), 7.55 (br.s, 1H), 7.34 (m, 5H), 6.13−6.05 (m, 1H), 5.88−5.78 (d, *J* = 10.4 Hz, 1H), 5.58−5.52 (m, 2H), 5.11−5.08 (m, 2H), 3.67−3.49 (m, 5H), 2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 166.1, 157.7, 155.0, 146.1, 136.1, 135.9, 128.3, 128.2, 127.8, 127.6, 120.4, 67.0, 58.5, 58.5, 51.3, 45.0, 44.6, 31.0, 30.5. Exact mass calcd for $C_{17}H_{20}N_2O_7Na^+$ $[M + Na]^+$, 387.1163 Found 387.1162.

Benzyl (2*S*,3*S*)-2-((*Z*)-3-Methoxy-3-oxoprop-1-en-1-yl)-3-((((7,7,7,7,7-pentafluoro-7λ^8-hepta-2,4,6-triynoyl)oxy)carbamoyl)oxy)pyrrolidine-1-carboxylate (32). To *N*-hydroxy carbamate **31** (1.07 g, 2.94 mmol) in CH_2Cl_2 (35 mL) at 0 °C was added NEt_3 (0.45 mL, 3.2 mmol, 1.1 equiv), followed by pentafluorobenzoyl chloride (0.42 mL, 3.0 mmol). The reaction was stirred at 0 °C for 15 min, diluted with sat. aq. NH_4Cl (30 mL), and transferred to a separatory funnel. The organic portion was removed, and the aqueous portion was extracted with additional CH_2Cl_2 (2 × 20 mL). The combined organic fractions were washed with sat. aq. $NaHCO_3$ (30 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel (elution: 20 → 80% EtOAc in hexanes) to afford the desired compound (**32**, 1.54 g, 94% yield) as a colorless oil: TLC (60% EtOAc in hexanes), R_f: 0.60 (UV, CAM): $[\alpha]_D^{25}$ = +66.1 (*c* 1.00, $CHCl_3$); IR (film) 3197, 2953, 2903, 1923, 1866, 1789, 1760, 1701, 1653, 1576, 1503, 1416, 1359, 1326, 1255, 1184, 1105, 998, 912, 818, 755, 697 cm^{-1}. The spectra of **32** are complicated by carbamate rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (br.s, 1H), 7.50−7.18 (m, 5H), 6.15−6.03 (dd, 1H), 5.94−5.83 (dd, *J* = 10.9 Hz, 1H), 5.74 (s, 1H), 5.63−5.58 (d, 1H), 5.14−5.07 (m, 2H), 3.83−3.14 (m, 5H), 2.35−2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 158.2, 155.0, 154.7, 145.7, 128.5, 128.3, 128.0, 127.7, 120.9, 104.7, 78.3, 67.2, 58.8, 51.4, 45.2, 31.1, 30.7. Exact mass calcd for $C_{24}H_{19}F_5N_2O_8Na^+$ $[M + Na]^+$, 581.0954 Found 581.0952.

Benzyl (4*R*,4a*S*,7a*S*)-4-((*R*)-1-Hydroxy-2-methoxy-2-oxoethyl)-2-oxohexahydropyrrolo[2,3-*e*][1,3]oxazine-5(2*H*)-carboxylate (38). Carbamate **32** (76 mg, 0.136 mmol) was dissolved in *t*-BuOH/water solution (3:1, 2.0 mL). In a separate vessel, a solution of $K_2OsO_4·H_2O$ (1.3 mg, 2.5 mol %) in water (0.5 mL) was added dropwise over 10 min. After stirring at rt under N_2 for 1.5 h, the reaction was quenched with addition of sodium sulfite (30 mg, 200 mg/mmol) and stirred for an additional 0.5 h. The solvent was azeotropically removed with toluene and chloroform and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel (elution: 0% → 10% MeOH in $CHCl_3$) to afford the desired aminohydroxylation product **38** (46 mg, 93% yield) as a colorless oil: TLC (5% MeOH in $CHCl_3$), R_f: 0.33 (UV, CAM); $[\alpha]_D^{25}$ = +44 (*c* 1.63, $CHCl_3$); IR (film) 3326, 3017, 2954, 2907, 1744, 1696, 1536, 1414, 1355, 1212, 1112, 759 cm^{-1}. The spectra of **38** are complicated by carbamate rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 6.93 and 6.77 (m, 1H), 5.13−5.06 (m, 3H), 4.77 (m, 1H), 4.47 and 4.29 (m, 2H), 4.02 (m, 1H), 3.83−3.72 (m, 3H), 3.53 and 3.48−3.41 (m, 2H), 2.20−2.16 and 1.99−1.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 155.5, 154.1, 136.0, 128.5, 128.2, 127.9, 79.2, 77.2, 72.8, 67.2, 53.8, 52.8, 44.7, 31.9. Exact mass calcd for $C_{17}H_{20}N_2O_7Na^+$ $[M + Na]^+$, 387.1163. Found 387.1162.

Benzyl (4*R*,4a*S*,7a*S*)-4-((*R*)-1,2-Dihydroxyethyl)-2-oxohexahydropyrrolo[2,3-*e*][1,3]oxazine-5(2*H*)-carboxylate. Aminohydroxylation product **38** (185 mg, 0.51 mmol) was dissolved in THF (5 mL) and cooled to 0 °C. A solution of $LiBH_4$ (3 M in THF, 0.50 mL, 1.5 mmol) was introduced via syringe. After stirring for 20 min, the reaction was diluted with sat. aq. NH_4Cl (10 mL) and brine (10 mL) and extracted with EtOAc (10 × 10 mL). The combined organic portions were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give 160 mg of a colorless oil. This residue was purified by flash chromatography on silica gel (elution: 0 → 15% MeOH in $CHCl_3$) to afford the desired diol compound (155 mg, 91% yield) as a colorless oil: TLC (5% MeOH in EtOAc), R_f: 0.25 (UV, CAM); $[\alpha]_D^{25}$ = +74.6 (*c* 2.00, CH_2Cl_2); IR(film) 3392, 2954, 2926, 2895, 1695, 1423, 1356, 1201, 1114, 1062, 971, 907 cm^{-1}. The spectra are complicated by carbamate rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H) 7.00−6.85 (br. s, 1H), 5.16 (d, *J* = 12.6 Hz, 1H), 5.07 (m, 1H), 5.05 (d, *J* = 12.6, 1H), 4.79 (m, 1H), 4.23 (m, 3H), 3.77 (m, 3H), 3.46 (m, 1H), 2.18 (m, 1H), 1.98 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 154.1, 135.9, 128.6, 128.2, 127.9, 79.0, 73.4, 67.5, 62.8, 53.9, 52.0, 45.1, 32.0; Exact mass calcd for $C_{16}H_{20}N_2O_6Na^+$ $[M + Na]^+$, 359.1214. Found 359.1213.

Benzyl (4*R*,4a*S*,7a*S*)-4-((*R*)-1,2-Bis((methylsulfonyl)oxy)-ethyl)-2-oxohexahydropyrrolo[2,3-*e*][1,3]oxazine-5(2*H*)-carboxylate. The starting diol (55 mg, 0.16 mmol) was dissolved in pyridine (1.5 mL), and MsCl (40 μL, 0.49 mmol) was added via syringe. After stirring at rt for 1.25 h, the reaction mixture was transferred to a separatory funnel and partitioned between $CHCl_3$ (10 mL) and H_2O/Brine (1:1, 10 mL). The organic portion was removed, and the aqueous portion was extracted with additional $CHCl_3$ (3 × 10 mL). The combined organic portions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel (elution: 75 → 100% EtOAc in hexanes) to afford the desired bismesylate (63 mg, 80% yield) as a colorless oil: TLC (EtOAc), R_f: 0.40 (UV, CAM); $[\alpha]_D$ = +52.0 (*c* 0.45, CH_2Cl_2); IR (film) 3366, 3268, 3032, 2939, 1707, 1422, 1358, 1175, 1117, 919 cm^{-1}. The spectra are complicated by carbamate rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 7.11 and 6.93 (m, 1H), 5.13 (m, 3H), 4.47 (m, 3H), 4.12 (m, 1H), 3.80 (m, 1H), 3.47 (m, 1H), 3.12 (m, 5H), 2.21 and 2.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 152.9, 135.9, 128.7, 128.6, 128.2, 127.9, 78.6, 78.5, 68.0, 67.4, 67.3, 53.8, 50.7, 49.4, 39.8, 37.6, 32.2; Exact mass calcd for $C_{18}H_{24}N_2O_{10}S_2Na^+$ $[M + Na]^+$, 515.0766. Found 515.0763.

5-Benzyl 3-(*tert*-Butyl)(4*R*,4a*S*,7a*S*)-4-((*R*)-1,2-bis((methylsulfonyl)oxy)ethyl)-2-oxotetrahydropyrrolo[2,3-*e*][1,3]-oxazine-3,5(2*H*,4*H*)-dicarboxylate (39). The bismesylated carbamate (57 mg, 0.12 mmol) was dissolved in THF (1.2 mL), and Boc_2O (40 μL, 0.18 mmol) and DMAP (10 mg, 0.08 mmol) were added successively. After stirring at rt for 1 h, the reaction mixture was diluted with sat. aq. NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic portions were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product **39** (70 mg, 98% yield) was obtained as a colorless oil. This material was used directly without purification: TLC (EtOAc), R_f: 0.75 (UV, CAM); $[\alpha]_D^{25}$ = +96.6 (*c* 0.85, CH_2Cl_2); IR (film) 2985, 2941, 2890, 1798, 1704, 1417, 1371, 1180, 1123, 972, 929 cm^{-1}. The spectra of **39** are complicated by carbamate rotamers. ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.30 (m, 2H), 5.13 (m, 2H), 5.00 (m, 1H), 4.47 (m, 2H), 3.12 (m, 6H), 2.26 (m, 1H), 2.16 (m, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 151.1, 147.6, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 68.0, 67.5, 66.9, 55.9, 55.4, 54.2, 45.1, 44.7, 38.9, 38.8, 37.8, 37.7, 32.8, 27.7; Exact mass calcd for $C_{23}H_{32}N_2O_{12}S_2Na^+$ $[M + Na]^+$, 615.1289. Found 615.1287.

Benzyl (2*S*,3*R*,3a*S*,6a*S*)-3-((*tert*-Butoxycarbonyl)amino)-2-(((methylsulfonyl)oxy)methyl)hexahydro-4*H*-furo[3,2-*b*]-pyrrole-4-carboxylate (40). The mixed imide **39** (20 mg, 0.034 mmol) was dissolved in MeOH (0.65 mL), and Cs_2CO_3 (11 mg, 0.034 mmol) was added in one portion. The reaction was stirred at rt for 2.5 h and concentrated to remove the bulk of MeOH. The residue was transferred to a separatory funnel and partitioned between $CHCl_3$ (10 mL) and H_2O/sat. aq. $NaHCO_3$ (1:1, 10 mL). The organic portion was removed, and the aqueous portion was extracted with additional $CHCl_3$ (2 × 5 mL). The combined organic portions were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield an amorphous solid (19 mg). This residue was dissolved in MeOH (1.0 mL), and $Pd(OH)_2$ (20 wt %

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on carbon, 11 mg) was added. The reaction vessel was flushed for 10 min with H_2 gas. The exit line was removed, and the reaction was stirred under an atmosphere of H_2 for 1.5 h (when the TLC indicated consumption of starting material). The reaction vessel was flushed with N_2, and the mixture was filtered through Celite. The filter pad was washed with aqueous 10% Na_2CO_3 (5 mL) and $CHCl_3$ (10 mL). The filtrate was transferred to a separatory funnel, and the organic portion was removed. The aqueous portion was extracted with additional $CHCl_3$ (3 × 5 mL). The combined organic portions were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel (elution: 0 → 5% MeOH in $CHCl_3$) to afford *N*-boc-norloline **20** (6 mg, 72% yield over 2 steps) as an amorphous solid. ^1H and ^{13}C NMR spectral data for **20** match previously prepared material[17] (see the Supporting Information): $[\alpha]_D^{25}$ = +35.8 (*c* 0.5, $CHCl_3$); *lit.* +38.7 (*c* 0.35).

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data (^1H NMR and ^{13}C NMR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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